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CASE REPORT

Ultrasound Features of Pediatric Kikuchi—Fujimoto Disease: Report of Two Cases

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Two pediatric cases of Kikuchi—Fujimoto disease (histiocytic necrotizing lymphadenitis) are reported due to its rarity. They came to clinical attention because of cervical lymphadenopathy and fever. One was diagnosed by open biopsy and the other by ultrasound-guided fine-needle aspiration biopsy. Ultrasonographic and histocytological findings are described. The importance of this entity is that it is easily confused clinically, radiologically and pathologically with malignant lymphadenopathy, especially lymphoma. Open biopsy is usually performed to obtain a definite diagnosis. However, when typical cytological findings are present, a precise diagnosis is possible and this allows clinicians to avoid unnecessary biopsies or aggressive treatment.

Introduction

Kikuchi—Fujimoto Disease (KFD) is a self-limited necrotizing lymphadenitis, and occurs predominantly in young Asia women and mainly presents with cervical lymphadenopathy [1]. KFD in children has different clinical manifestations compared to that in adult populations [2,3]. In the pediatric population, KFD shows completely different gender predominance. The diagnosis of KFD is based on clinical manifestations, fine-needle aspiration (FNA) cytology or excision biopsy. The pathological characteristics include patchy paracortical lymphohistiocytic aggregates with variable karyorrhexis and absence of granulocytic infiltration. Typical cytological features include apoptotic nuclear debris and histiocytes in adequately sampled [4,5]. Antibiotics are not helpful and symptoms generally subside spontaneously within 6 months.

The importance of this entity lies in the fact that it can be easily confused clinically, pathologically and radiologically with malignancy, especially lymphoma. Biopsies are

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commonly done for histological diagnosis; when typical cytological findings are presented, a precise diagnosis is possible [4,5]. The use of ultrasound (US) and appearance of KFD in pediatric patients has not been well described before. The authors advise the awareness of this clinical manifestations and image features of KFD in children. US-guided FNA (US-FNA) cytology may be helpful to avoid unnecessary investigations and inappropriate or aggressive treatment.

Case presentations

Case 1

A 7-year-old boy presented with spiking fever (up to 39 °C), mild cough, and sore throat, with left-side neck pain for 8 days before hospitalization. There was no rhinorrhea, nausea, vomiting, abdominal pain, diarrhea, flank pain, dysuria or myalgia. Clinical history did not reveal any travel, exposure to animals, or insect bites. On admission, physical examination disclosed multiple movable, tender, enlarged lymph nodes on the left side of the neck, axillary and inguinal regions. Examination of other systems was normal. A complete blood count showed normal white blood cell count (5320/μL), and elevated C-reactive protein and lactate dehydrogenase level (4.817 mg/dL and 736 mg/dL, respectively). Throat/rectal viral swabs or throat culture did not show any abnormal findings. Chest X-ray and urinalysis were unremarkable. Azithromycin, ampicillin/sulbactam, and vancomycin plus clindamycin were used but fever persisted without resolution.

Neck sonography was done using an ATL HDI 5000 with a high-resolution 7.5—12-MHz real-time linear-array transducer (Philips Ultrasound, Bothell, WA, USA). Multiple homogeneous hypoechoic confluent lymph nodes at the posterior triangle (level V) were found (Fig. 1). Cortical enhancement was shown (arrow). Echogenic hilus was absent. The tentative impression was benign reactive lymphadenopathy. As a result of persistence of the neck nodes and fever, excision of an enlarged lymph node was done and sent for pathology, *Mycobacterium tuberculosis* polymerase chain reaction (TB PCR), and Gram stain examination.

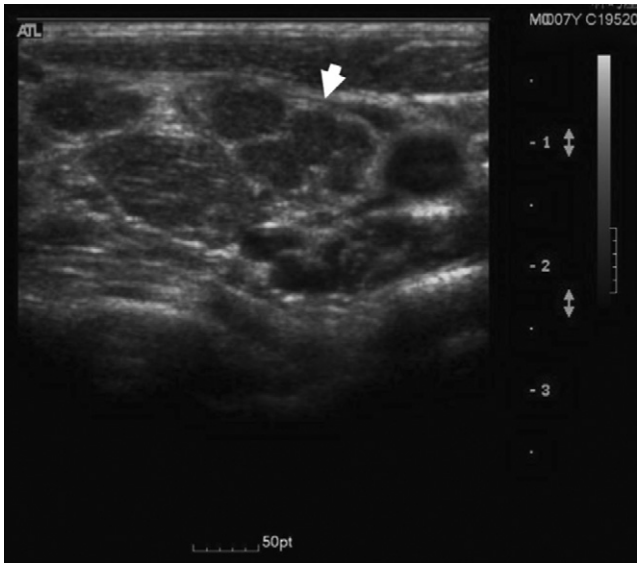

Fig. 1 Axial ultrasound scan at left posterior triangle demonstrated multiple, hypoechoic, enlarged confluent lymph nodes with hyperechoic rims (arrow).

Both results of TB PCR and Gram's stain were negative for pathogens. Histological examination showed abundant histiocytes, karyorrhexis and no neutrophils (Fig. 2). Histological findings, together with the clinical data, were consistent with histiocytic necrotizing lymphadenitis or KFD. Methylprednisolone sodium succinate (2 mg/kg/day) was prescribed and fever subsided dramatically. After 3 months, he made a completely recovery and has remained asymptomatic during 6 months' follow-up.

Case 2

An 8-year-old boy denied a history of travel, exposure to animals, and insect bites. He presented with swelling on the right side of the neck for 1 day, and was brought to our outpatient department for further evaluation. Episodes of fever were mentioned 1 week before this visit. On examination, mucopus in the nasal cavities with postnasal drip was found with a 3 cm × 3 cm, movable, tender lymph node in the level II region of the right neck. The remainder of the examination was unremarkable. Neck US was arranged and showed matted nodes measuring up to 1.1 cm × 3.2 cm in the right upper neck (level II). The nodes were ovoid in shape, homogeneous in internal echo, hypoechogenic, lacked vascular signal or calcification, and had an echogenic hilus. Under the guidance of real-time US, FNA (Fig. 3) was performed and cytological examination (Fig. 4) showed many nuclear fragments with clusters of proliferating histiocytes. The cytological features were consistent with KFD. Symptomatic care was given, fever subsided, and cervical lymphadenopathy disappeared spontaneously 3 months later, without other signs or symptoms of disease. He has remained asymptomatic during 6 months' follow-up.

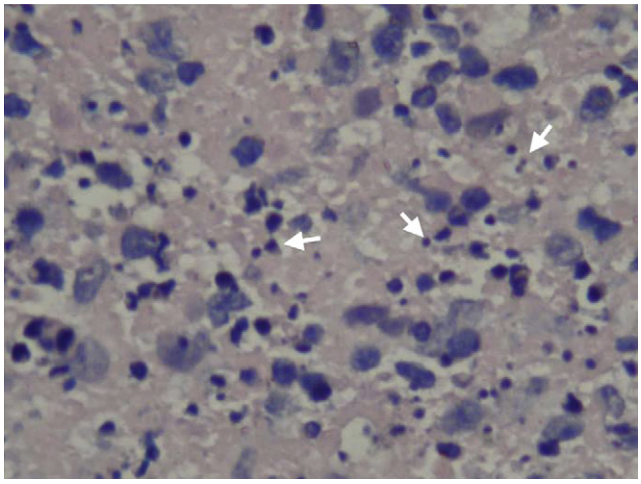

Fig. 2 Histopathology showed fibrinous necrosis with frequent apoptosis and many nuclear fragments (karyorrhexis, arrows), but an absence of neutrophils (hematoxylin and eosin stain, 400×).

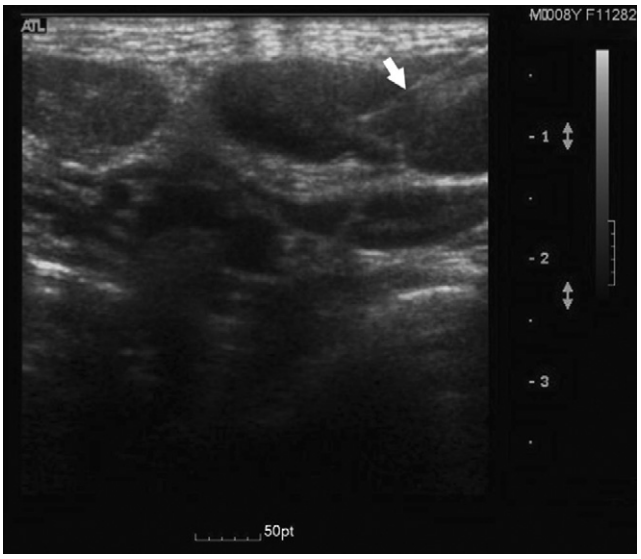

Fig. 3 Fine needle (arrow) aspiration was done under the real-time guidance of ultrasound. Sonography showed matted, enlarged lymph nodes with hyperechoic rims.

Discussion

KFD is a histiocytic necrotizing lymphadenitis, which was described for the first time in Japan in 1972, almost simultaneously by Kikuchi and Fujimoto [6,7]. It most commonly affects adults younger than 40 years of age and mainly in the Asian population, but has been reported in all races. Early studies have noted a female predominance, but recent reports have shown only a small female preponderance. However, in the pediatric population, KFD has been found to be more prevalent in boys than in girls (male/female, 1.4—2.8:1) [2,3,8].

Although there is some indication that it may be associated with viral infection or autoimmune disease, the pathogenesis of KFD is still unclear, and culture, special staining and serological testing have failed to reveal significant evidence. The onset of KFD is usually acute or subacute, developing over a period of 2—3 weeks. Patients most often present with asymptomatic lymphadenopathy (52%) and with lymphadenopathy and fever [9]. The most commonly involved site is the cervical lymph nodes (56—98% of cases). Rarely, patients have associated constitutional symptoms such as weight loss, diarrhea, chills, or sweats. In most cases, the disorder resolves spontaneously in an average of 1—4 months. Most patients with this disorder have no associated illnesses; some children with KFD will develop systemic lupus erythematous later, and they should be closely followed for the possible development of autoimmune disease.

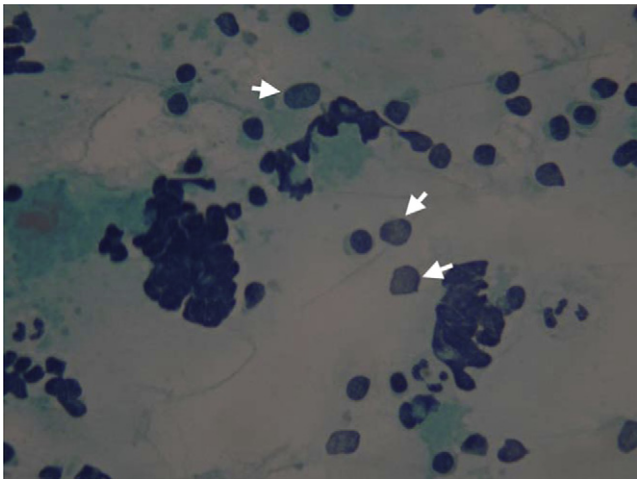

Fig. 4 Cytology of Kikuchi—Fujimoto disease demonstrated lymphoid cells showing variable apoptotic degeneration. Abundant proliferating histiocytes (arrows) was also seen (Liu's stain, 400×).

No specific laboratory tests contribute to the diagnosis of KFD. Mild leukopenia has been seen in 20—58% of patients. Computed tomography (CT), US and magnetic resonance imaging do not yield features that distinguish KFD from other diseases that commonly involve lymph nodes, such as lymphoma, tumor metastases, or tuberculosis. The gold standard for making an accurate diagnosis is excisional biopsy with histological examination or typical cytological features [4]. The chief pathological features of KFD are variable degrees of necrosis in cortical and paracortical areas, with prominent karyorrhectic debris (nuclear fragmentation), proliferation of histiocytes and immunoblasts surrounding the area of necrosis, and absence of neutrophils. Clinically and histologically, KFD is often mistaken for lymphoma or systemic lupus erythematosus. Cytologically, absent atypia with a polymorphous lymphoid population, abundant karyorrhectic debris and histiocytes are characteristic features of KFD [4,5].

The most frequently reported imaging modality for KFD is CT [10]. The common features of CT scans in KFD are unilateral, homogeneous enlargement of multiple lymph nodes affecting levels II—V. Perinodal infiltration on CT scans has been mentioned in previous reports [10,11]. It has also been observed in other nodal diseases, including lymphoma and metastasis; however, perinodal infiltration is more characteristic of inflammatory diseases. Histologically, structures surrounding the lymph nodes are infiltrated by an attenuating perivascular and interstitial inflammatory cell population similar to that seen in nodal-based lesions. This population includes a mixture of lymphoid cells and histiocytes and the characteristic karyorrhectic debris.

On US, the enlarged matting nodes exhibit a homogeneous or heterogeneous texture and are surrounded by a thick irregular zone that is hyperechoic relative to the lymph node itself [9,12,13]. The hyperechoic rims consist of perinodal infiltration in histological examination or CT. Matting of nodes is another characteristic of KFD [9,13]. Histological examination has found that matting of lymph nodes is also associated with perinodal inflammatory reaction. Matting is more common in tuberculous nodes and is possibly due to periadenitis and adjacent soft-tissue edema [14]. Matting was found in both of our cases.

The differential diagnosis of a patient with KFD includes lupus lymphadenitis, reactive lymphadenitis, tuberculous lymphadenitis, malignant lymphoma, and metastatic malignancy. On US, the lupus adenopathy is generalized, indicating a systemic process [15]. Most small well-defined lymph nodes with ovoid shape and echogenic hilus are

suggestive of reactive nodes. Tuberculous nodes feature round nodes with matting, intranodal cystic necrosis and perinodal swelling [16], whereas enlarged nodes with round shape, reticulation and posterior enhancement are indicative of lymphomatous nodes [17]. Metastatic nodes are characterized by ill-defined, round nodes with intranodal necrosis. However, there is still an overlap in the US features of these diseases and KFD. The diagnosis of KFD depends on a high index of suspicion and is confirmed through clinical observation, US examination, and histological or cytological specimens with characteristic features.

US-FNA of enlarged lymph nodes in children is a safe, reliable procedure that often obviates the need for an excisional biopsy [18]. The accurate diagnosis of KFD on FNA cytology is possible, given correct clinical data and well-prepared specimens [4,5]. FNA cytology can be attempted initially before open biopsies; the overall diagnostic rate of FNA cytology for KFD has been estimated to be around 56.3%, [19] therefore, half the patients can avoid unnecessary investigations and inappropriate or aggressive treatment. However, if the sonogram is not characteristic or only FNA cytology is done, careful evaluation of clinical presentations and course may still be important for definite diagnosis.

KFD is usually a benign and self-limited disease lasting from 1 to 4 months. There is no specific treatment for KFD and, in general, therapy is targeted toward symptomatic relief, including relief of fever and lymph node tenderness with use of analgesics and antipyretics. Corticosteroids are reserved for severe cases or relapsing disease. A low recurrence rate has been described in 3—4% of cases [20] and may occur as late as 8—9 years, and in one case even 16 years, after initial diagnosis. Long-term follow-up is mandatory for the risk of evolution into an autoimmune syndrome.

In conclusion, KFD is a benign self-limiting disease. Neck US examination combined with US-FNA cytology may help in identifying pediatric KFD of the neck and avoid unnecessary investigations and inappropriate or aggressive treatment.

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